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10/069,145	02/22/2002	Manja Ahola	TUR-125	7684

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EXAMINER
DI NOLA BARON, LILIANA

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,145	AHOLA ET AL.	
	Examiner	Art Unit	
	Liliana Di Nola-Baron	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 8-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Regarding claims 8-16, the limitation "the xerogel is derived from a tetraalkoxysilane and that part of the tetraalkoxysilane is replaced by an organomodified alkoxysilane" in lines 4-6 of claim 8 renders the claims indefinite, because it is not clear what is meant by the word "derived" and the phrase "that part". Furthermore, if the xerogel claimed by Applicant is prepared from a tetralkoxysilane, said xerogel cannot be prepared from an alkyl-substituted alkoxysilane, as claimed by Applicant, unless the tetraalkoxysilane and the alkyl-substituted alkoxysilane are both in the same mixture. For the purpose of examination, the examiner will interpret the claims according to their broadest reasonable interpretation consistent with the specification, which teaches that the xerogel is derived from a tetraalkoxysilane and part of the tetraalkoxysilane is replaced by an organo-modified alkoxysilane (See p. 6). Accordingly, the examiner will interpret the claims as directed to compositions and method comprising a xerogel formed from a reaction mixture comprising alkoxysilane and alkyl-substituted alkoxysilane.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 8-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (U.S. Patent 5,858,280) in view of Pinchuk et al. (U.S. Patent 5,804,318).

Zhang et al. discloses a method for preparing methyl-modified silica gel using the sol-gel technology, and teaches that the modified silica gel produced by the method of the invention have a three-dimensional network structure, which allows doping optically functional substances in high concentrations (See col. 2, lines 10-67).

Zhang et al. teaches that a methyltrialkoxysilane, such as methyltriethoxysilane, may be combined with a tetraalkoxysilane, such as tetraethoxysilane, or a dialkoxysilane, such as dimethyldiethoxysilane,to control the size and polarity of spaces defined by the polysiloxane network (See col. 3, lines 1-15).

Thus, with respect to the compositions claimed in claims 8-10 of the instant application, the prior art discloses modified silica gels obtained from a sol-gel and comprising a tetraalkoxysilane and an alkyl-substituted alkoxysilane, as claimed in claim 8, and a biologically active agent, wherein

the tetraalkoxysilane is tetraethoxysilane, as claimed in claim 9, and the alkyl-substituted alkoxysilane is methyltriethoxysilane, as claimed in claim 10.

With regard to the biologically active agent claimed in claims 8 and 11 of the instant application, Zhang et al. is deficient in the sense, that the patent does not provide heparin or a related acidic polysaccharide in the gel compositions of the invention and fails to disclose the concentration of the active agent in percentage by weight, as claimed by Applicant in claim 11. However, the prior art teaches that the size of space defined by the polysiloxane network of the invention is particularly suitable to dope optical agents in high concentration (See col. 2, line 58 to col. 3, line15), thus the patent provides the general teachings that gels formed from compositions comprising tetraethoxysilane and an alkyl-substituted alkoxysilane are suitable carriers for biologically active agents.

With regard to the limitation in claim 8, that a carrier is a xerogel, Zhang et al. does not define the gels of the invention as xerogels, however, the patent contemplates drying the gel, as it teaches that the gel of the invention is less susceptible to volumetric shrinkage upon drying (See col. 2, lines 48-51). A xerogel is a dry polymerized gel, thus the patent contemplates producing silica xerogel carriers, as claimed by Applicant.

With respect to the method claimed in claims 12-16 of the instant application, Zhang et al. provides a method for preparing the modified silica gel of the invention, comprising perfoming a hydrolysis reaction by adding an amount of water to the starting material comprising

methyltriethoxysilane and tetraethoxysilane at acidic or neutral pH in the presence of an acid to promote the reaction, removing alcohols produced by the hydrolysis reaction and adding a metal complex, such as (acetylacetonato) aluminum (III), a biologically active agent, to the mixture during the hydrolysis reaction (See col. 3, line 1 to col. 4, line 4 and Example 10). The patent teaches that the hydrolysis reaction of the invention includes not only the hydrolysis of alkoxysilyl group to silanol group, but also the subsequent polycondensation (polymerization) reactions of silanol groups with alkoxysilyl groups (See col. 3, lines 22-26). Zhang et al. does not specifically mention that water is removed after hydrolysis, however, the patent teaches that alcohols are removed by evaporation (See col. 3, lines 36-38). It is the view of the examiner that exposure of the hydrolysis product to evaporation would cause the water present in the mixture to evaporate.

Thus, with respect to claim 12, Zhang et al. provides a method comprising hydrolyzing an alkoxysilane and an organo-modified alkoxysilane in the presence of a catalyst, adding a biologically active agent , allowing the hydroxysilane to polymerize and removing water and alcohol produced as by-product by evaporation. As stated above, with regard to the biologically active agent claimed in claim 12 of the instant application, Zhang et al. is deficient in the sense, that the patent does not provide heparin or a related acidic polysaccharide in the gel compositions produced by the method of the invention. However, the prior art teaches that metal complexes, such as (acetylacetonato) aluminum (III), a biologically active agent, are added to the mixture during the hydrolysis reaction (See col. 3, line 39 to col. 4, line 4 and Example 10). Furthermore, the patent teaches that the compositions produced by the method of the invention

are particularly suitable to dope optical agents in high concentration (See col. 2, line 58 to col. 3, line15), thus the patent provides the general teachings that gels formed from compositions comprising tetraethoxysilane and an alkyl-substituted alkoxysilane are suitable carriers for biologically active agents and may be produced by the method of the invention.

Regarding the tetraalkoxysilane claimed in claim 13 and the alkyl-substituted alkoxysilane claimed in claims 14 and 15 of the instant application, Zhang et al. teaches that the starting material for the hydrolysis reaction comprises methyltriethoxysilane and tetraethoxysilane or dimethyldiethoxysilane (See col. 3, lines 1-15 and Example 10). Thus, the patent provides an alkoxysilane and an alkyl-substituted alkoxysilane, as claimed by Applicant.

With regard to the catalyst claimed in claim 16 of the instant application, Zhang et al. teaches that the hydrolysis reaction is performed in the presence of an acid, such as nitric acid or acetic acid, to promote the reaction (See col. 3, lines 16-22). Thus, the patent contemplates a method for preparing the gels of the invention, comprising adding a catalyst to the reaction mixture, as claimed by Applicant.

Thus Zhang et al. provides the general teachings that gels formed from compositions comprising tetraethoxysilane and an alkyl-substituted alkoxysilane are suitable carriers for biologically active agents and may be produced by the method of the invention. As stated above, with regard to the biologically active agent claimed in claims 8-16 of the instant application, Zhang et al. is deficient in the sense, that the patent does not provide heparin or a related acidic polysaccharide

in the gel compositions and method of the invention. Additionally, with respect to claim 11, the patent fails to disclose the concentration of the active agent in percentage by weight, as claimed by Applicant.

Pinchuk et al. provides a hydrogel coating bondable to an epoxy-functionalized surface of a medical device and comprising anti-thrombogenic agents (See col. 2, line 18 to col. 3, line 1). The patent teaches that the epoxy groups are provided by a trifunctional silane, which may be reacted with the polymer of the hydrogel (See col. 2, lines 59-65), thus the reference provides hydrogel compositions comprising a trifunctional silane. The patent includes ethoxysilanes among the silane agents, which can be used in the invention (See col. 4, lines 40-46) and discloses heparin sulfate as the anti-thrombogenic agent in the hydrogel compositions, teaching that the heparin slowly releases with time into the surrounding body fluids to prevent clotting (See col. 5, lines 13-21). In Example 3, the patent teaches that an epoxy-functionalized silane-primed catheter is dipped into a hydrogel solution comprising 2% heparin.

Thus, with regard to claims 8, 11 and 12 of the instant application, the patent provides the general teachings, that hydrogel compositions comprising ethoxysilanes may comprise heparin as anticoagulant agent, which is then released from said compositions.

With respect to claim 11, Pinchuk et al. provides hydrogels comprising 2% heparin. The patent is deficient in the sense, that the reference fails to disclose an amount of 5-30%, calculated on the air-dried xerogel, as claimed by Applicant. Zhang et al. contemplates drying the gel, as the

reference teaches that the gel of the invention is less susceptible to volumetric shrinkage upon drying (See col. 2, lines 48-51). A xerogel is a dry polymerized gel. It is the view of the examiner that during the process of air-drying, the gel looses water and concentration of the solutes in the gel increases as a result of the water loss. Thus, the 2% concentration of heparin sulfate disclosed by Pinchuk et al. in the wet hydrogels of the invention will increase to a higher percentage, when calculated on the air-dried xerogel.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the gel compositions and method for producing said compositions disclosed by Zhang et al., by including heparin in the gel compositions of the invention, as taught by Pinchuk et al., to obtain a composition for the controlled release of heparin. The expected result would have been a successful gel composition for the controlled release of heparin and a successful method for preparing said composition. Because of the teachings of Zhang et al., that the gels formed from compositions comprising tetraethoxysilane and an alkyl-substituted alkoxysilane are useful as carriers for biologically active agents and are resistant to drying, and the teachings of Pinchuk et al., that hydrogel compositions comprising ethoxysilanes are useful as carriers for the controlled release of heparin, one of ordinary skill in the art would have a reasonable expectation that the compositions and method claimed in the instant application would be successful in providing a carrier system for the controlled release of heparin. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

6. Claims 8-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuncova et al. (Collect. Czech. Chem. Commun.) in view of Pinchuk et al. (U.S. Patent 5,804,318).

The paper by Kunkova et al. discloses xerogels prepared using sol-gel procedures by hydrolysis of silicon alkoxides (See Abstract and p. 1573), and specifically includes tetraethoxysilane (TEOS), methyltriethoxysilane (METES) and dimethyldiethoxysilane (DMDES) among the alkoxides used in the research (See Solution IV in Table 1, p. 1574). Thus, with respect to the carrier claimed in claims 8-10 of the instant application, the prior art provides xerogels derived from sol-gels and comprising tetraethoxysilane and alkyl-substituted alkoxysilanes, specifically methyltriethoxysilane and dimethyldiethoxysilane, as claimed by Applicant.

With regard to the biologically active agent claimed in claims 8 and 11 of the instant application, Kuncova et al. is deficient in the sense, that the paper does not provide heparin or a related acidic polysaccharide in the xerogel compositions and fails to disclose the concentration of the active agent in percentage by weight, as claimed by Applicant in claim 11. However, the prior art teaches that lipase, a biologically active agent, is immobilized in xerogel compositions and retain its activity for an extended period of time (See pp. 1574-1576 and Table 2). In particular, the reference teaches that the xerogel formed from solution IV, comprising TEOS and DMDES, is characterized by a higher activity of lipase as compared to other xerogels obtained from compositions not comprising the tetraethoxysilane or the alkyl-substituted alkoxysilane (See p. 1574, Table 1 and Table 2). Thus, the prior art provides the general teachings that xerogels

formed from compositions comprising tetraethoxysilane and an alkyl-substituted alkoxysilane are suitable carriers for biologically active agents.

Pinchuk et al. provides a hydrogel coating bondable to an epoxy-functionalized surface of a medical device and comprising anti-thrombogenic agents (See col. 2, line 18 to col. 3, line 1). The patent teaches that the epoxy groups are provided by a trifunctional silane, which may be reacted with the polymer of the hydrogel (See col. 2, lines 59-65), thus the reference provides hydrogel compositions comprising a trifunctional silane. The patent includes ethoxysilanes among the silane agents, which can be used in the invention (See col. 4, lines 40-46) and discloses heparin sulfate as the anti-thrombogenic agent in the hydrogel compositions, teaching that the heparin slowly releases with time into the surrounding body fluids to prevent clotting (See col. 5, lines 13-21). In Example 3, the patent teaches that an epoxy-functionalized silane-primed catheter is dipped into a hydrogel solution comprising 2% heparin. Thus, with regard to claims 8 and 11 of the instant application, the patent provides the general teachings, that hydrogel compositions comprising ethoxysilanes may comprise heparin as anticoagulant agent, which is then released from said compositions.

With respect to claim 11, Pinchuk et al. provides hydrogels comprising 2% heparin (See Example 3). The patent is deficient in the sense, that the reference fails to disclose an amount of 5-30%, calculated on the air-dried xerogel, as claimed by Applicant. A xerogel is a dry polymerized gel. It is the view of the examiner that during the process of air-drying, the gel looses water and concentration of the solutes in the gel increases as a result of the water loss.

Thus, the 2% concentration of heparin sulfate disclosed by Pinchuk et al. in the wet hydrogels of the invention will increase to a higher percentage, when calculated on the air-dried xerogel.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the xerogel compositions disclosed by Kuncova et al., by including heparin in the gel compositions of the invention, as taught by Pinchuk et al., to obtain a composition for the controlled release of heparin. The expected result would have been a successful gel composition for the controlled release of heparin. Because of the teachings of Kuncova et al., that xerogel compositions prepared using sol-gel procedures by hydrolysis of silicon alkoxides, specifically TEOS, METES and DMDES, are useful as carriers for biologically active agent, and the teachings of Pinchuk et al., that hydrogel compositions comprising ethoxysilanes are useful as carriers for the controlled release of heparin, one of ordinary skill in the art would have a reasonable expectation that the compositions and method claimed in the instant application would be successful in providing a carrier system for the controlled release of heparin. Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Liliana Di Nola-Baron whose telephone number is 703-308-8318. The examiner can normally be reached on Monday through Thursday, 5:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 308-1234/ 1235.

Liliana Di Nola-Baron

August 24, 2003

Liliana Di Nola-Baron
Patent Examiner
Art Unit 1615